REMARKS

Claims 1, 3 to 27, 39 to 43, and 62 to 81 are pending in this application. Applicants have cancelled claim 2 as redundant, and cancelled claims 28 to 38 and 44 to 61 without prejudice as directed to non-elected inventions or a non-elected species (claim 28), and have amended claims 1, 12, 13, 24, 39, and 41 to clarify the claims and correct typographical errors. These amendments add no new matter. Applicants have also added new claims 62 to 81 based on claims as originally filed, and on concepts described throughout the application. For example, the concept of assessing the thickness of the fibrous cap by analyzing variation of τ as a function of distance from a center of the speckle pattern as a function of $(x_o^2+y_o^2)^{1/2}$ is described in the application, e.g., at page 16, lines 8-10. The concept of measuring collagen content or determining viscosity of a lipid pool is described in the application, e.g., at page 15, lines 11-22. Measuring biomechanical properties of the tissue in three dimensions is described, e.g., at page 17, lines 18-23. The new claims accordingly add no new matter.

Applicants appreciate the Examiner's conclusion that claim 26 would be allowable if rewritten in independent form, but submit that all of the pending claims are allowable for the reasons discussed below.

The Invention

The invention is based on the discovery that tissues can be analyzed *in vivo* using laser speckle to measure microscopic motion, such as Brownian motion or cellular motion, of structures and characteristics within the tissue.

In general, the invention features a method of analyzing tissue by illuminating a tissue with coherent light, such as laser light, or partially coherent light; receiving light reflected from the tissue and forming a series of speckle patterns; and analyzing changes in the speckle patterns at time intervals sufficient to measure changes caused by motion of objects within the tissue on a microscopic motion scale.

Specification

Applicants have amended the title to more closely relate to the presently pending claims.

Claim Interpretation

Applicants acknowledge that the Office Action states (at page 2),

> [i]t is noted on page 10 of the specification that time intervals "sufficient to detect microscopic Brownian motion" for atherosclerotic plaque are about "1-200 ms."
>
> On page 11 the examiner notes that the PR interval of the diastole of a heartbeat lasts about "0.12-0.2 seconds, providing sufficient time to detect Brownian motion."

Applicants submit that those of skill in the relevant field understand that Brownian motion varies depending on the type of tissue analyzed. For example, Brownian motion of calcified tissue may require a time interval of about 1 second to be detected. The application at page 10 provides an exemplary time interval range of 1 to 200 ms to detect Brownian motion in atherosclerotic plaques, but this is not the complete range of useful time intervals to detect Brownian motion.

35 U.S.C. § 102

Claims 1 to 6, 12, 14 to 16, 21 to 23, 25, 27, and 28 have been rejected as being allegedly anticipated by Vachon et al. Applicants respectfully traverse this rejection for the following reasons.

According to the Office Action (at page 3), Vachon describes a method for analyzing stress and strain in atherosclerotic plaque by

> illuminating artery regions with coherent or partially coherent light (e.g., infrared light, col. 5 lines 38-44; also incorporating by reference its parent application disclosing functional theory of laser speckle interferometry), receiving reflected light to form a series of speckle patterns (col. 2 lines 27-58), and analyzing changes in the speckle patterns (col. 3 lines 3-14) at time intervals "sufficient" (i.e., in real time, during diastole) to measure changes "caused by" microscopic motion of objects within tissue (inherently including Brownian and cellular

motion). Vachon et al. further teaches digitizing and quantitatively correlating the speckle patterns to a reference pattern (col. 2 lines 39-45, claim 6). Vachon et al. additionally discloses video camera (18) which obtains real time speckle data. See also figures 1 and 3 and claims 1-5.

Applicants submit that Vachon's methods compare a signal received from a body in a reference state with a signal from the body when it is undergoing, or has undergone, deformation. For example, to measure changes in coronary arteries, Vachon plots the boundaries of the artery at the end of diastole and midsystole (col. 3, lines 40-44) or systole (col. 4, line 46), and measures elasticity by analyzing "the rate of strain which is the ratio of the *change in dimension of the body* to the original dimension per unit time" (col. 4, lines 27-33, emphasis added).

As described in the present application, two common sources of *macroscopic* motion are gross movement of the vessel lumen and plaque tissue due to heartbeats, and blood flow between the plaque and the catheter. Thus, it is clear that the change in diameter of an artery, such as the coronary artery, between diastole and systole, i.e., **a change in dimension of the body**, is **macroscopic motion**. Thus, Vachon looks at macroscopic, not microscopic, motion, and certainly not Brownian or cellular motion. Thus, Vachon does not anticipate applicants' claims.

Furthermore, applicants respectfully submit that even if Brownian or cellular motion occurs "inherently" in the blood vessels, as the Examiner states, there is simply no indication anywhere in Vachon that he analyzes "changes in the speckle patterns at time intervals sufficient to measure changes caused by microscopic motion of objects within the tissue" as required by the claims. To the contrary, Vachon is not measuring Brownian or cellular motion, because that data would not show a change in the dimension of the artery, and thus could not indicate the rate of strain of the coronary artery.

Accordingly, Vachon does not anticipate applicants' independent claim 1, or claims 2 to 6, 12, 14 to 16, 21 to 23, 25, 27, or 28, which depend from claim 1.

35 U.S.C. § 103

Claims 7-11, 13, 18-20, 24, 39, and 40 have been rejected as being allegedly unpatentable over Vachon et al. in view of Kirkpatrick et al. or Moreno et al. Applicants respectfully traverse this rejection for the following reasons.

The Office Action concedes that Vachon "does not explicitly address invasively obtaining near field speckle data," but asserts that, Kirkpatrick and Moreno use direct (i.e., intravascular) laser speckle/interferometric data (via e.g., catheter) to effect earlier detection of structural changes pertaining to atherosclerosis and thereby more accurately determine appropriate courses of action. The Office Action concludes (at page 4) that

> It would have been obvious at the time the invention was made to a person of ordinary skill in the art to directly obtain optical speckle/interferometric data with (e.g., a catheter) for artherosclerotic [sic] plaque analysis as taught by Kirkpatrick et al. or Moreno et al. in the invention as taught by Vachon et al. to more accurately assess the status of the intravascular plaques and determine appropriate courses of action thereby reducing procedure complication rates.

Applicants respectfully disagree, because neither Kirkpatrick nor Moreno fills the gap in Vachon's disclosure.

First, Moreno does not even relate to the use of speckle patterns to analyze tissue. Instead, Moreno describes the use of near-infrared spectroscopy to analyze vulnerable atherosclerotic plaques.

Second, rather than analyzing microscopic Brownian or cellular motion, Kirkpatrick teaches away from analyzing this microscopic motion in tissues. In fact, Kirkpatrick states, "[m]any of the difficulties in applying speckle methods to soft tissue arise from the cellular and Brownian motion of scattering particles within the tissue" (at page 121). To remove this "difficulty," Kirkpatrick uses a strain measurement technique, similar to Vachon, and samples at a rate that is fast enough "to ensure that the observed speckle motion is due to the imposed strain, and *not simply due to cellular and Brownian motion*" (at page 124, emphasis added). It is precisely this cellular and Brownian motion that applicants have discovered is not a difficulty at all, but can be used to provide valuable information about a tissue.

Thus, applicants respectfully submit that even if one of skill in this field were to combine Vachon with Kirkpatrick and/or Moreno, the result would be some type of strain measurement, with the goal of avoiding the very measurements of microscopic motion of objects within the tissue that applicants are claiming in the present application. Thus, none of these references, either singly or in combination, describe or even suggest the invention covered by the pending claims.

Claims 17 and 41-43 have also been rejected as being allegedly unpatentable over Vachon in view of Kirkpatrick or Moreno, and further in view of Boas. Applicants traverse this rejection for the following reasons.

The Office Action concedes that Vachon, Kirkpatrick, and Moreno all fail to describe calculations of decorrelation rates and comparisons to mathematical simulation models. In an attempt to remedy this deficiency, the Office Action cites Boas to provide the general teaching of comparing optical tissue properties (taking into account the decorrelation rate) to mathematical simulation models such as Monte Carlo and diffusion theory "to more easily and accurately predict and derive tissue structure data on a microscopic level (p. 468-472 and 475)"(Office Action at page 5). The Office Action then concludes that "it would have been obvious at the time the invention was made to a person of ordinary skill in the art to compare the optical speckle data of Vachon et al. in view of Kirkpatrick or Moreno with mathematical simulation data as taught by Boas et al. to verify results and to derive more accurate tissue structure data on a smaller scale" (at page 5). Applicants disagree.

As noted above, both Vachon and Kirkpatrick describe methods of analyzing arteries using applied strain, and measuring changes in speckle patterns as the strain rate changes. Vachon is silent about Brownian and cellular motion, but it is clear that Vachon is not interested in measuring this microscopic motion. Kirkpatrick goes even further, and actively avoids measuring this microscopic motion of objects within the tissue.

Boas et al. describes the use of a correlation diffusion equation to model the transport of temporal field correlation in diagnosing the thickness of burned tissue. There is simply no suggestion in Boas et al. to use their methods to make strain measurements of arteries. Similarly,

there is no suggestion in either Vachon or Kirkpatrick to use the mathematical models of Boas et al. in their methods. More importantly, even if one of skill in the art were to combine all of these different references for the generic reasons proffered in the Office Action, the result would not be the claimed invention. Thus, the combination of references cited in the Office Action would not have rendered the present claims obvious at the time of the invention.

Applicants therefore respectfully request that the Examiner reconsider and withdraw all prior art rejections and allow the claims.

CONCLUSION

All of the pending claims are allowable, which action is respectfully requested. Please apply any charges or credits to deposit account 06-1050 referencing attorney docket number 00786-443001.

Respectfully submitted,

Date: 10-7-04

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